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Case Series Evaluating Lymphocyte Subgroups at Diagnosis and After Treatment in Multisystem Inflammatory Syndrome Associated with COVID-19 in Children

Çocuklarda COVID-19 ile İlişkili Multisistem Enflamatuvar Sendromunda Tanı Esnasında ve Tedavi Sonrasında Lenfosit Alt Gruplarının Değerlendirildiği Vaka Serisi

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Abstract

Objective: In this case series, we aimed to examine the changes in lymphocyte subgroups in children diagnosed with the multisystem inflammatory syndrome (MIS-C) during the acute phase and in the first month after treatment.

Material and Methods: Ethics committee approval was received for the study from the Ethics Committee of Ondokuz Mayıs University patient data were analyzed from medical records in an electronic database. Initial immunological evaluations of our first five patients diagnosed with MIS-C were made, steroid and IVIG treatments were given to the patients, and lymphocyte subgroups were evaluated for the second time in the first month for control purposes.

Results: In MIS-C cases, it was observed that lymphopenia was severe in the acute period, CD3 T cells decreased, the ratio of 2:1 between cytotoxic T cells and helper T cells was impaired, B cells increased proportionally, and NK cells were normal or decreased. When we evaluated MIS-C cases with the control lymphocyte subgroup in the first month, it was observed that lymphopenia improved and CD3 T cells increased proportionally, and active T cells decreased to normal values in the first month after treatment. On the other hand, while naive B cells decreased, non-switching and switching B cells increased and NK cells decreased.

Conclusion: While COVID-19 is an acute infection, MIS-C is associated with cytokine storm induced by the acute infection. Immunologic assessment of MIS-C cases is considered important since the condition causes immune

Öz

Giriş: Bu vaka serisinde, multisistem enflamatuvar sendrom (MIS-C) tanısı alan çocukların akut fazı sırasında ve tedaviden sonraki birinci ayda lenfosit alt gruplarındaki değişikliklerin incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışma için etik kurul onayı Ondokuz Mayıs Üniversitesi Klinik Araştırmalar Etik Kurulundan alınmıştır. Hasta verileri elektronik bir veri tabanındaki tıbbi kayıtlardan analiz edilmiştir. MIS-C tanılı ilk beş hastamızın ilk immünolojik değerlendirmeleri yapıldı, hastalara steroid ve IVIG tedavileri verildi ve kontrol amaçlı olarak birinci ayda ikinci kez lenfosit alt grupları değerlendirildi.

Bulgular: MIS-C vakalarında akut dönemde lenfopeninin ağır olduğu, CD3 T hücrelerinin azaldığı, sitotoksik T hücre ve yardımcı T hücre arasındaki 2:1 oranın bozulduğu, B hücrelerinin oransal olarak arttığı, NK hücrelerinin normal ya da azaldığı görülmüştür. MIS-C vakalarını birinci ayda kontrol lenfosit alt grup ile değerlendirdiğimizde ise lenfopeninin düzeldiği, oransal olarak CD3 T hücreleri arttığı aktif T hücrelerinin tedavi sonrasında birinci ayda normal değerlere düştüğü görülmüştür. Diğer taraftan naif B hücreleri azalırken *non-switch* ve *switch* yapan B hücrelerinin arttığı, NK hücrelerinin düştüğü görülmüştür.

Sonuç: COVID-19 akut bir enfeksiyon iken MIS-C akut enfeksiyonun tetiklediği sitokin fırtınasıyla ilişkilidir. Konak immün sisteminde immün disregülasyona sebep olması nedeniyle MIS-C vakalarının immünolojik açıdan değerlendirmeye alınmasını önemli olduğu düşünülmektedir. MIS-C'nin erken teşhisinde lenfopeni, B hücre artışı, CD4/CD8 oranı-

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dysregulation in the host immune system. Lymphopenia, increased B cell count, reversal of the CD4/CD8 ratio, and increased active T cell count may be beneficial in the early diagnosis of MIS-C. Since it is thought that the cytokine storm causes complications in MIS-C, immediate administration of IVIG treatment is considered essential. Although it was demonstrated that the disease manifests with marked cellular changes, there is still a need for further studies.

Keywords: Multisystem inflammatory syndrome, intravenous immunoglobulin, lymphocyte subgroup

hücrelerinin artması yararlı olabilir. MIS-C'de komplikasyonlara sitokin fırtınasının sebep olduğu düşünüldüğü için IVIG tedavisinin hemen uygulanmasının önemli olduğu düşünülmektedir. Hastalığın seyrinde hücresel olarak belirgin değişikliklerin olduğu gösterilse de konu ile ilgili daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Multisistem enflamatuvar sendrom, intravenöz immünglobulin, lenfosit alt grubu

Introduction

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection is typically mild and often asymptomatic in children. In April 2019, i.e., the first peak of the COVID-19 pandemic, in Europe a group of pediatric patients was found to exhibit COVID-19 related clinical symptoms that resembled symptoms of Kawasaki disease and toxic shock (1). It was observed that the signs and symptoms were associated with COVID-19 but developed 2-4 weeks after the acute phase of the disease, wherein the antibody or serology tests showed positive results for COVID-19 (1). The pathogenesis of this newly described disease was uncertain, but the disease had similar characteristics as Kawasaki disease. The disease was suggestive of vasculitis and associated with a possible autoimmune etiology. The clinical signs and symptoms consisted of fever, rash, conjunctivitis, peripheral edema, gastrointestinal symptoms, shock, and increased levels of acute-phase reactants and cardiac markers. The disease was considered a new multisystem inflammatory syndrome, and with the increase in awareness, it has been reported more frequently in children (MIS-C) in Europe and the United States (2,3). Since the disease is thought to cause complications by leading to cytokine storms, immediate administration of intravenous immunoglobulin (IVIG) treatment is deemed important, and it is also essential to emphasize that IVIG treatment leads to marked cellular changes. In this case series, the immunological differences between the acute phase and the first month of the disease, and the importance of IVIG treatment are emphasized.

Case 1

A 15-year-old male patient presented with abdominal pain, constipation, fever, and cough that had been present for two days. His elder sister had been diagnosed with COVID-19 through a polymerase chain reaction (PCR) test and had received treatment at home 1.5 months ago. At that time, the patient had no symptoms suggestive of COVID-19. Abdominal computed tomography (CT) was performed since the patient had abdominal pain. The patient was thought to have pancreatitis. Physical examination revealed neck stiffness, tenderness in the abdomen, strawberry tongue, and chapped lips. PCR test result was negative for COVID-19; however, antibody test was positive and chest CT was found to be consistent with COVID-19 pneumonia. Echocardiography showed decreased left ventricular motion, an EF of 42% and 3.2 mm and 3.3 mm of left and right coronary artery diameters, respectively.

Case 2

A nine-year-old male patient presented with fever, abdominal pain, headache, and diarrhea that had been present for five days, followed by a rash, conjunctivitis, and cervical lymphadenopathy. Therefore, the patient was considered to have atypical Kawasaki disease. There was no known family history of COVID-19 or close contact with a positive patient. However, it was understood that one of the patient's neighbors had received treatment for COVID-19 six weeks ago. The patient's PCR test resulted negative for COVID-19 twice; however, the antibody test yielded positive results. Chest CT revealed diffuse atelectasis in both lungs. Physical examination showed abdominal tenderness and the patient was found to have marked edema in the jejunal loop wall, increased peristalsis, and 1.5 cm fluid in the deepest part of the pelvis on ultrasound examination. The patient was followed up in the intensive care unit since his blood pressure was closer to the lower limits. Echocardiography showed a 19 mm tubular aneurysm in the left coronary artery.

Case 3

A seven-year-old female patient was referred to us with a preliminary diagnosis of Kawasaki disease with complaints of fever, abdominal pain, red eyes, and chapped lips. The patient's elder sister was found to be positive for COVID-19 according to a PCR test performed 20 days ago. The patient tested negative for COVID-19 according to a PCR test; however, the antibody test was positive. Physical examination revealed abdominal tenderness, conjunctival hyperemia, and strawberry tongue. The patient also had diarrhea and abdominal pain. Echocardiography performed at another center showed coronary artery prominence and an EF of 54%.

Table 1. Demographic characteristics of MIS-C cases

	Case 1	Case 2	Case 3	Case 4	Case 5
Patient's age	15 years	9 years	7 years	5 years	9 years
Gender	Male	Male	Female	Female	Female
Height	50-75 p	<3 p	50-75 p	50 p	50 p
Weight	97 p	10-25 p	>97 p	97 p	75-90 p
Comorbidity	Obesity	-	Obesity	-	-
COVID	+	-	+	-	-
Stay in hospital	11 day	12 day	9 day	10 day	4 day
Intensive care hospitalization	-	3 day	-	-	-
COVID disease in the family	+	+	+	+	+
1.PCR	-	-	-	-	-
2.PCR	-	-	-	-	-
Antibody IgG, IgM	+	+	+	+	+
Respiratory viral panel	-	-	-	-	-
PA AC graphy	Bilateral infiltration	Bilateral	Bilateral	Bilateral	Nonspecific opacity
Thorax computed tomography	Peripheral ground glass density, fibrotic changes	Slight ground glass in both lungs, parenchymal thickening and atelectasis in the right lung			

Table 2. Laboratory findings of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Hb (g/dL)	12.1	10.5	11.4	12.2	12.4
WBC (mm^3)	12030	10950	12190	5440	6620
Lymphocyte (mm^3)	1090	710	1080	730	1070
Neutrophil (mm^3)	10330	9740	10270	4390	5390
Monocyte (mm^3)	540	260	730	270	150
Basofil (mm^3)	30	20	40	10	10
Eosinophil (mm^3)	40	220	70	40	0
PLT (mm^3)	96000	171000	177000	148000	172000
CRP(mg/dL)	440	208	111	133	116
Sedimentation (mm/h)	100	10	80	42	140
D dimer (ng/mL)	6991	7191	6679	5860	4850
CPK (U/L)	61	43		554	
CK-MB (U/L)		1.48	0.89	2.07	1.24
Troponın I (ng/mL)	0.6	0.13	0.19	0.1	0.1
LDH (U/L)	268	310	311	472	250
Procalcitonin (ng/mL)	5.2	42	0.2	5.6	3.48
Ferritin (ng/mL)	688	398	1165	555	695
AST(U/L)	35	25	37	102	29
ALT (U/L)	32	21	18	80	30
Creatinine (mg/dL)	1.01	0.67	0.56	0.47	0.43
Na (mEq/L)	132	124	131	137	134
Albumin (gr/dL)	3	2.8	3.2	2.2	3.2

Hb: Hemoglobin, Hct: Hematocrit, WBC: White blood cell, PLT: Platelet, CRP: C reactive protein, CPK: Creatine kinase, LDH: Lactate dehydrogenase, AST: Aminotransferase test, ALT: Alanine aminotransferase.

Table 3. Treatments of MIS-C cases

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Metilprednisolone	+	+	+	+	+
IVIG	2 gr/kg	2 gr/kg	2 gr/kg	2 gr/kg	2 gr/kg
Antiviral	-	+	-	+	-
Anticoagulant	+	+	+	+	-
Aspirin	-	+	+	+	-
Anakinra	-	-	-	-	-
Antibiotic	+	+	+	+	+
Inotropic agent	+	-	-	-	-
Echocardiography	Myocarditis	Left coronary dilatation	Myocarditis	-	-
Abdominal USG	Pancreatitis	Fluid, edema, hepatomegaly	Fluid	Normal	Normal

IVIG: Intravenous immunoglobulin, USG: Ultrasonography.

Table 4. Lymphocyte subgroup of patients diagnosed with MIS-C at baseline and at one month

	P1b	P1a	P2b	P2a	P3b	P3a	P4b	P4a	P5b	P5a
Lymphocyte %	%19↓ (21-43)	%26	%15 ↓ (29-47)	%23↓	%17↓ (21-51)	%32	%14↓ (32-59)	%50	%24↓ (29-47)	%38
CD3 T	%21 ↓↓ (62-81)	%65	%43↓ (60-79)	%56↓	%29↓↓ (61-84)	%41	%48 ↓ (57-77)	%65	%51↓ (60-79)	%62
CD3CD4 T	%13↓ (31-53)	%35	28%↓ (29-48)	%34	18%↓ (26-53)	%30	30% (26-46)	%33	%30 (29-48)	%32
CD3CD8 T	%8↓ (19-30)	%31	15%↓ (18-33)	%22	10%↓ (19-35)	%27	18% (16-33)	%32	%20 (18-33)	%28
CD19 B	%32↑ (6-21)	%30↑	23%↑ (8-21)	%19	33% (8-23)	%13	% 38 ↑↑ (12-25)	%13	%37 ↑↑ (8-21)	%6 ↓
CD3-CD56 NK	%6 (6-23)	%0↓↓	11% (8-22)	%9	%1↓↓ (6-21)	%5	8% (6-21)	%15	%3 ↓↓ (8-22)	%4 ↓↓
Naive helper T	%34 (31-57)	%31	53% (25-63)	%44	73% (32-68)	%54	57% (35-69)	%72↑	%67↑ (25-63)	%72↑
Naive cytotoxic T	%95 ↑↑ (18-61)	%54	57% (22-58)	%51	64%↑↑ (7-26)	%41	65% (23-68)	%50	%80↑↑ (18-61)	%60
CD19+CD27-IgD+Naive	%90 ↑ (65-88)	%71	53%↑ (64-84)	%29↓	77% (51-85)	%39	75% (65-86)	%62↓	%87 (65-88)	%67
Non-switched B cell	%1 ↓↓ (4-12)	%13↑	25%↑ (4-14)	%34↑	7% (5-17)	%15	12% (5-16)	%9	%5 (4-14)	%10
Switched B cell	%4 (4-16)	%12	14% (6-16)	%23↑	6% (5-22)	%13	%3↓ (4-16)	%8	%4↓ (6-16)	%13
CD19 + CD38 + CD21low	%0↓ (2-6)	%2	1%↓ (2-7)	%0↓	5% (2-10)	%3	6%↓ (3-10)	%10	%0↓ (2-7)	%3

B: Before IVIG, A: After IVIG.

Case 4

A five year-old female patient presented to another center with fever, nausea, and lack of appetite. The patient underwent a PCR test after her mother tested positive for COVID-19. The patient was then referred to us due to persistent fever and rash. The patient tested negative for COVID-19 in two PCR tests; however, the COVID-19 antibody test was positive. During follow-up, the patient, who had a left coronary artery diameter of 3 mm, had frequent vomiting and developed strawberry tongue and conjunctivitis. Thrombocytopenia worsened during follow-up. The patient was followed up for macrophage activation syndrome.

Case 5

A nine-year-old female patient presented with fever, diarrhea, and rash that blanched when pressed. She was treated for urinary tract infection due to smelly urine and detection of leukocyte esterase positivity in a urinalysis performed at another center. However, the patient had a persistent fever and a PCR test was performed, since her mother was COVID-19-positive one month ago. Physical examination of the patient revealed conjunctivitis, strawberry tongue, and diffuse macular rash. The antibody test yielded positive results.

Discussion

It is known that COVID-19 had a milder clinical course in most children, unlike adults. The multisystemic inflammatory syndrome was first identified in London in eight children presenting with fever, rash, conjunctivitis, peripheral edema, and gastrointestinal symptoms. Later, the number of reported cases of MIS-C started to increase after an improved awareness and increased incidence of COVID-19. Most children can survive with a rapid diagnosis and intervention, but the long-term consequences of MIS-C are still unclear. According to a review, the most common signs and symptoms reported during MIS-C consisted of abdominal pain (61.9%), vomiting (61.8%), skin rash (55.3%), diarrhea (53.2%), hypotension (49.5%), and conjunctivitis (48.4%), and particularly gastrointestinal (90.9%), cardiovascular (86.5%), or dermatological or mucocutaneous (70.9%) involvement (2). In addition, cardiac dysfunction (40.6%), shock (35.4%), myocarditis (22.8%), coronary artery dilatation, aneurysm (18.6%), and acute kidney injury (18.4%) were also observed. Most of the patients (63.9%) were admitted to an intensive care unit and the median length of stay at the intensive care unit was five (3-7) days (2). Of the tests performed on 565 (99.1%) patients due to suspected SARS-CoV-2, all tests yielded RT-PCR or serology-positive results, wherein 46.1% of the patients only had serologic evidence of infection and 25.8% only had positive RT-PCR results. In most patients, initial echocardiography was normal, followed by suppression of ejection fraction or enlargement of the coronary arteries or aneurysm manifesting a few days later (2). In our ongoing study, gastrointestinal symptoms, fever, and rash were the common symptoms in all patients. In this case series, three patients had cardiac involvement, one of whom required admission to the intensive care unit and received inotropic support. All the patients had a history of contact with people who were COVID-19-positive and developed complaints four to six weeks later. While lymphopenia was a warning sign, there was an increase in CRP, sedimentation, D-dimer, and ferritin levels in blood biochemistry.

Gastrointestinal findings of the patients were prominent. One patient had pancreatitis in the abdominal ultrasonography findings, and the other two patients had significant intra-abdominal fluid. In the literature, there are cases of acute appendicitis, acute abdomen and cases diagnosed with MIS-C later. Two patients had myocarditis and one patient had coronary aneurysm. The most important complications of MIS-C are cardiac complications, and it is very important in determining the mortality of the patients. Methylprednisolone and IVIG treatments were administered to the patients as soon as they were diagnosed. Although the patients exhibited a severe clinical picture, they rapidly provided a clinical response. In addition, early administration of IVIG treatment is believed to affect treatment response in multisystemic inflammatory syndrome (4).

Although lymphopenia was common in adult patients with COVID-19, the degree of lymphopenia was associated with disease severity. With the evaluation of lymphocyte subgroups in studies, it was reported that CD4 T cell, CD8 T cell, B cell, NK cell, and total lymphocyte counts all exhibited a statistically significant decrease in patients with severe/critical COVID-19 compared to those with mild/moderate disease. This was shown to be associated with the severity of the disease (5). However, lymphopenia was milder in pediatric patients, as shown in the current study and previous studies. On the other hand, significant lymphopenia was observed in pediatric patients who were found to have the multisystemic inflammatory disease. Therefore, we also evaluated the lymphocyte subgroups of these patients. Additionally, in this case, series, lymphocyte subgroups were evaluated at the time of diagnosis and month one after the administration of IVIG treatment, and it was aimed to underline the differences between these evaluations.

In the acute period; severe lymphopenia, decreased CD3 T cells, impaired 2:1 ratio between cytotoxic T cells and helper T cells, It was observed that B cells increased proportionally and NK cells were normal or decreased. In the first month, lymphopenia improved, CD3 T cells increased proportionally, naive B cells decreased, non-switched and switched B cells increased, NK cells decreased, overactive T cells returned to normal.

In the literature, when MIS-C is compared with pediatric COVID-19, MIS-C patients had higher proportions of HLA-DR + CD38 + CD4 + and CD8 + T cells (6). In this case series, it was observed that while helper T cells decreased in MIS-C, cytotoxic T cells increased and the ratio of 2:1 between them was impaired, NK and NKT cells decreased, and active T cells (CD3 + CD38 + HLA DR) increased. Although lymphopenia is present, it is seen that T cells are mainly affected.

Moreover, although naive B cells increase in the acute period, switch and non-switching B cells are rare. On the other hand, NK and NKT cells were decreased in MIS-C cases. These data suggest that it is associated with the activation of both innate and native lymphocytes in MIS-C.

IVIG is a blood product containing polyclonal IgG. IVIG treatment is used in Kawasaki disease and in various diseases that particularly involve autoimmunity, due to its immunoregulatory and antibody-binding effects. It is known that IVIG treatment prevents cytokine storms when included in the treatment protocols for patients who are considered to have MIS-C. Therefore, it was observed that the disease-related overactive T cells returned to normal values during the treatment period and with IVIG treatment according to the evaluations performed at the time of diagnosis and month one (7).

Antigen presentation, expression of proinflammatory cytokines, apoptosis, differentiation and maturation of immune cells, antibody-dependent cellular cytotoxicity, phagocytosis, and regulation of T cell population can be achieved as a result of the interaction of Fc gamma receptors and IgG-Fc found in almost all immune cells. IVIG treatment, which is known to have an immunomodulatory effect at high doses, in COVID-19 patients with severe disease criteria; It has been suggested that it reduces the cytokine storm by targeting and that it does this through clearance of complement, inhibition of innate immune cells, effector T cell activation and proliferation of T regulatory cells (8).

We have the opinion that it is important to perform an immunologic assessment including lymphocyte subgroups and immunoglobulin values in pediatric patients presenting with severe symptoms of COVID-19 and MIS-C before administration of IVIG and/or steroid treatment. Studies on this topic are still ongoing in Türkiye and at our center, and further information will be provided in the future.

We believe our results-will be useful to guide the diagnosis, treatment, and follow-up processes of the MIS-C patients. Larger groups of further studies are needed.

Ethics Committe Approval: Ethical approval was obtained from Ondokuz Mayıs University Clinical Research Ethics Committee (Decision no: B.30.2.ODM.0.20.08/602-728, Date: 19.11.2020).

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